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10/602,141	06/23/2003	Aaron K. Sato	10280-058001	7569

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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 02/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/602,141	SATO ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32,34-40,46,48,50 and 58-74* is/are pending in the application.

4a) Of the above claim(s) *9,10,15-32,34-40,46,48,50,58-63,72 and 73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11-14,64-71 and 74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' election is noted for the following species: 1) Intramolecular disulfide bond. 2) Dipeptide. Applicants elect a species in which the peptide includes an aromatic dipeptide sequence. 3) Co-extensive. 4) Integrin with respect to claim 37. Election of a target molecule (integrin) was previously made in the telephonic interview of January 18, 2005 and made of record. 5) With a conjugated moiety. 6) With a cytotoxic moiety. 7) Kunitz domain. As explained above, all pending claims currently under examination read on the elected species. Applicants emphasize that many of the claims are generic with respect to the species and encompass the elected and non-elected species. For example, claim 25 encompasses both a protein that includes a cytotoxic moiety and one that does not include a cytotoxic moiety.

Applicants respectfully request that the Examiner withdraw the restriction requirement with respect to Groups I, II, and III. First, as stated in MPEP 803, if the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions.

Applicants submit that the Examiner has not provided any reason why it would be burdensome to examine the claims of Groups I, II and III together. In fact, a first Office Action was issued by the Patent Office, prior to the present restriction requirement. For that Office Action, original claim 1 was searched and examined. Original claim 1 was broader in scope than the presently pending claims 1, 3, and 65. There cannot be an undue burden in examining presently pending claims 1, 3, and 65 in the instant application if original claim 1, which was broader in scope than claims 1, 3, and 65, has already been searched.

In view of applicants' arguments and upon reconsideration of the restriction requirement, the restriction with respect to Groups I-III has been withdrawn. Also, the species restriction made therein. (Note the election of Integrin as made in the last Office action is however maintained.)

Newly submitted claims 72 and 73 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims examined in the previous Office action does not include a scaffold domain, let alone variants of the scaffold domain. Since applicant has received an action on the merits for the originally presented invention, this invention has been

constructively elected by original presentation for prosecution on the merits. Accordingly, claims 72 and 73 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Status of Claims

Claims 1-32, 34-40, 46, 48, 50 and 58-74 are pending.

Claims 9-10, 15-32, 34-40, 46, 48, 50,58-63 and 72-73 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claims 1-8, 11-14, 64-71 and 74 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 11-14, 64-71 and 74, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter

The as-filed specification does not provide support for a plurality of at least 10^{2} diverse proteins. MPEP 714.02 clearly states that applicants should point out where in the specification support for the amended limitation appears.

Written Description

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

The specification fails to describe a method of identifying a phage-binding protein and serum albumin comprising providing a plurality of at least 10^{2} diverse proteins comprising a region encoded by a degenerate oligonucleotides and identifying the members of the plurality. The specification, specifically the Examples, does not describe the claimed method steps. It does

not describe a step for a protein that can contain a region of degenerate oligonucleotides or the length and kind of degeneracy in the oligonucleotides. There is no method step that describes binding of a protein containing said region to a target. It describes at pages 58-59, Example 1 and Example 2, the peptide DX-954 isolated by phage display and its binding to VEGF-R2 and the prevention of serum albumin binding of the peptide to VEGF-R2. It is not apparent as to how the peptide is obtained from a 102 diverse protein comprising a region of degenerate oligonucleotides to show possession of the method. The specification describes in general terms and/or provides a laundry list of the different methods and/or components that can be employed by the method. A "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967). Thus, it is not apparent from the laundry list of components and method how the protein containing binding peptide is obtained. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show

that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). In biotechnological applications one cannot make a priori statement due to the uncertainty involve in experiments involving biological compounds as nucleotides and proteins. For example, it is well known in the art, that it is often difficult to know where insertions in the protein for mutations(peptide) encoded by oligonucleotides can be done without deleteriously affecting the protein function or its global structure. The diversity of the inserts is not easily estimated. It may be for example, that only a small subset of possible peptide sequences are presented efficiently by a particular expression system. And, it is not always easy to follow the expression of peptides in particular cells; for example, to know whether or not a specific cell is expressing a member of the insert, especially for biological methods. While this approach appears attractive, there are numerous problems, including difficulties of enriching positive clones from phage libraries. Enrichment procedures are based on

selective binding and elution onto a solid surface such as an immobilized receptor. Unfortunately, avidity effects arise due to multivalent binding of the phage and the general tendency of phage to contain two or more copies of the displayed polypeptide. The binding to the receptor surface therefore does not depend solely on the strength of interaction between the receptor and the displayed polypeptide. This causes difficulties in the identification of clones with high affinity for the receptor; thus, there remain distinct deficiencies in the methods used to isolate and screen polypeptides, particularly antibodies, even in view of the development of phage libraries. Georgiou (USA 5,866,344 at col. 2, lines 1-23). It is not possible to predict which predetermined (variations) of amino acids would result in the desired random mutant with a desired binding effect. It is generally known that the conformational freedom that promotes binding, e.g., by modifying the peptides into the protein sequences, might be restricted which may likely perturb the function and stability of the protein in ways difficult to predict and measure. Some proteins accommodate insertions (variations) at numerous sites throughout their primary sequence. Others are much less accommodating. It is difficult in general to predict which proteins are robust to insertions, and which sites in a particular protein are best

suited to insertion of multiple independent sequences. The complex spatial configuration of amino acid side chains in proteins and the interrelationship of different side chains in the randomized sites are insufficiently understood to allow for such predictions. Selective (site-directed) mutagenesis and saturation mutagenesis are of limited utility for the study of protein structure and function in view of the enormous number of possible variations in complex proteins. There are still no rules that have emerged that allow structure to be related to sequence in any simple fashion (even as applied to the actual compounds). See e.g., Murray (USP 2003/0104591) at e.g., paragraphs [0271]-[0272].

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 64-71 and 74, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 64 it is unclear as to the limitation of a "protein comprise varied consecutive positions". Does this refer to the entire protein structure or to the region of degenerate oligonucletoide? This rejection has similar import to claim 65.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the

reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 3, 5, 6, 7, 11, 12, 14, 64, 69, 70-71 and 74, as amended, are rejected under 35 U.S.C. 102(b) as being anticipated Sjobring (Infection and Immunity).

Sjobring discloses at e.g., page 3601 a method of identifying a protein that binds to a target as IgG and serum album comprising providing a display library of proteins in a cell and identifying the protein. The two broad claimed method steps employing broad components of e.g., display library is fully met by the process of Sjobring.

Claims 1-8, 11-13, 64-71 and 74, as amended, are rejected under 35 U.S.C. 102(a) as being anticipated by Sato et al (20050250700).

Sato discloses at paragraph [0008] polypeptides and compositions useful for detecting and targeting primary receptors on endothelial cells for vascular endothelial growth factor (VEGF), i.e., vascular endothelial growth factor receptor-2 (VEGFR-2, also known as kinase domain region (KDR) and fetal liver kinase-1 (Flk-1)), and for imaging and targeting complexes formed by VEGF and KDR. Sato discloses at paragraph [0393] that when the binding peptides disclosed are used as therapeutic

agents, it may be advantageous to enhance the serum residence time of the peptides. This can be accomplished by conjugating to the peptide a moiety, such as a fatty acid, that binds non-covalently to serum proteins, especially serum albumin, and/or fusing DNA that encodes the KDR-binding peptide to DNA that encodes a serum protein such as human serum albumin. In paragraph [0522] it is disclosed that in selecting the parental binding domain or template on which to base the variegated amino acid sequences of the library, the most important consideration is how the variegated peptide domains will be presented to the target, i.e., in what conformation the peptide analogues will come into contact with the target. In phage display methodologies, for example, the analogues will be generated by insertion of synthetic DNA encoding the analogues into phage, resulting in display of the analogue on the surfaces of the phage. Such libraries of phage, such as M13 phage, displaying a wide variety of different polypeptides, can be prepared using techniques as described, e.g., in Kay et al. See the specifics of the method in the Examples.

Claims 14, 65, 69-70 and 74, as amended, are rejected under 35 U.S.C. 102(b) as anticipated by Buettner (USP 5,834,318). Buettner discloses a method of identifying a protein that binds

to a target by providing a library of hexamer peptide library. This hexamer peptide obtained from oligonucleotides or random sequences. The peptide is identified by interacting with a protein target e.g., Factor IX with HSA mixtures. See.e.g, col. 4, lines 5-35. See also, the Example at col. 8. Accordingly, the process steps of broad scope are fully met by the specific process steps of Buettner employing specific components therein. It is considered that the interaction with human serum albumin would be inherent to the method since the solution contains both the target and the serum albumin.

Claims 1-8, 11-14, 64-71 and 74 as amended, are rejected under 35 U.S.C. 102(e) as anticipated Rondon et al (USP 6,919,424).

Rondon discloses a method of identifying a protein that binds to a target by providing a library of peptide of 10^{2} diverse proteins. The peptide is identified by interacting with a protein target e.g., CEA containing serum albumin. See.e.g., col. 8, lines 34-39; col. 9, line 5 up to col. 24, line 19. It is considered that the interaction with human serum albumin would be inherent to the method since the solution contains both the target and the serum albumin.

Accordingly, the specific process steps of Rondon fully meet the claimed method.

Claims 3, 5-8 and 14, as amended, are rejected under 35 U.S.C. 102(b) as being anticipated by Yousif et al (APMIS) for reasons set forth in the last Office action.

Response to Arguments

Applicants argue that with the amendments to claim 1 reciting a plurality of at least 102 diverse proteins, Yousif does not apply.

In response, while amendment to claim 1 has been overcome however, Yousif anticipates the now amended independent claim 3. Yousif at page 891, col. 2, Materials and Methods describes a method of identifying a protein that binds to a target and to human serum albumin comprising contacting a plurality of diverse proteins such as Nptase, protein A, histone f3, avidin and lysozyme with antibodies (Ig) and Human serum albumin (page 893, paragraph bridging col. 1 and col. 2 up to page 894, col. 1.) and then determining the proteins that bind to the Ig and human serum albumin. See further page 895, paragraph bridging col. 1 and 2 up to page 896, col.2. Accordingly, the specific process steps of Yousif using specific components therein fully meet the broad claimed method steps using components of broad of no define structure.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8, 11-14, 64-71 and 74, as amended, are rejected under 35 U.S.C. 103(a) as being obvious over Buettner (USP 5,834,318) in view of Sato et al (Biotechnol. Prog.) and Burger et al (Int. J. Cancer).

Buettner is discussed above. Buettner does not disclose a phage display of the proteins (claims 3-4), the in vivo half life of the identified member(as recited in claim 2), invariant cys residues (claim 13). However, Sato discloses at page 182, col.1 the numerous desirable properties of phage display in identifying protein binding target (i.e., ligand). For example, phage display allows one to rapidly screen several billion peptide sequences against a protein target and binders can be selected iteratively and the other disclosed desirable properties. See page 185 as to the amino acid sequences of the peptide being less than 30 and a cyclic peptide. Also, page 185,

RESULTS and DISCUSSION section as to the advantage of cyclic peptide over linear peptide. Sato also discloses that human serum albumin, the most abundant protein in serum, serves as a metabolite/drug transporter, inter alia, as to its numerous uses. Burger discloses at page 718 the in vivo half-life determination of a compound containing human serum albumin. Its determination will show whether a compound is rapidly and efficiently cleared from a body of a patient. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to replace the conventional method of Buettner with phage display as taught by Sato for the advantages derived from said phage display. The numerous advantages provided by phage display would motivate one to its use. Also, to determine the half-life of the identified target binding proteins of Buettner would have been obvious as taught by Burger. The motivation is to determine how rapidly or efficiently a compound is cleared from the system.

Claims 1-8, 11-14, 64-71 and 74 as amended, are rejected under 35 U.S.C. 103(a) as being obvious over Rondon et al in view of Sato et al (Biotechnol. Prog.) and Burger et al (Int. J. Cancer).

Rondon is discussed above. Rondon does not positively recite interaction (although is considered inherent to the

method, as discussed above) with HSA. However, Sato discloses that human serum albumin, the most abundant protein in serum, serves numerous functions or uses e.g., as a metabolite/drug transporter, inter alia. Burger discloses at page 718 the in vivo half-life determination of a compound containing human serum albumin. Its determination will show whether a compound is rapidly and efficiently cleared from a body of a patient. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to positively use serum albumin or determine the usefulness of serum albumin in the method of Rondon as taught by Sato for the numerous uses of serum albumin. The numerous uses of serum albumin would provide the motivation to one having ordinary skill in the art as to the binding effect of the peptide to its target and to the most abundant component of serum, albumin. Also, to determine the half-life of the identified target binding proteins of Buettner would have been obvious as taught by Burger. The motivation is to determine how rapidly or efficiently a compound is cleared from the system.

Claims 1-8, 11-14, 64-71 and 74, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Rondon or Buettner in view of Sato et al (Biotechnol. Prog.) and Burger et

al (Int. J. Cancer) and further in view of Rouslahti. [This rejection is based on the elected target species, integrin].

Buettner and Rondon does not disclose the target as integrin. However, Rouslahti discloses at col. 1, lines 25-33 that integrins control many medically important biological phenomena, such as cell migration in development, tissue repair, cancer cell differentiation, platelet aggregation and homing of immune system cells and neuronal processes. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use integrin as a target in the method of Buettner or Rondon as taught by Rouslahti. One would have been motivated to determine integrin as a target because of its numerous effects or medical biological phenomena, specifically its effect on cancer cells.

In view of the amendments to the claims and applicants' arguments, the rejection of the claims under 35 USC 103 over Yousif no longer applies.

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is

reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

This application contains claims 9-10, 15-32,34-40, 46, 48, 50, 58-63 and 72-73 drawn to nonelected inventions. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw

January 21, 2006